REMARKS

The Official Action dated February 21, 2002 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place this application in condition for allowance. Reconsideration is respectfully requested.

Submitted herewith is a Declaration Under 37 C.F.R. 1.132 by the coinventors. The Declaration is unsigned, as the original Declaration is currently being executed by the coinventors. Once the executed Declaration is received by the undersigned, it will be immediately forwarded to the Examiner. Consideration of the unsigned Declaration until the executed Declaration is filed is respectfully requested.

By the present Amendment, claims 1 and 30 are amended to more clearly describe the controlled sustained release of the claimed compositions. Claim 30 is also amended to include a phrase which was inadvertently omitted in Applicants' first amendment of claim 30. A Version With Markings Showing Changes Made is attached. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claim Rejections - 35 U.S.C. §103(a)

Claims 1-30 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Lowey et al U.S. Patent No. 3,870,790 in view of Stupak et al U.S. Patent No. 5,162,117, and also in view of Takashima et al U.S. Patent No. 4,853,249. The Examiner continues to rely on Lowey et al to teach a combination of pharmaceutical active and carrier of hydroxypropylmethyl cellulose (HPMC), or hydroxypropylmethyl cellulose and ethylcellulose (EC). The Examiner also asserts that Lowey et al teach release of active over a prolonged period of time. Stupak et al is relied upon for teaching various excipients in the pharmaceutical art. Takashima et al is relied upon to teach that cellulose derivatives are

known in the art to be interchangeable and useful either alone or in combination as a binder in a sustained release composition.

This rejection is again traversed and reconsideration is respectfully requested as the combination of teachings of these three cited references does not suggest the presently claimed invention. None of the references, either alone or in combination, teach a composition with each and every element as presently recited in the claims, together with the improved properties thereof. The references must suggest the desirability and thus the obviousness of making the claimed combination, *In re Grabiak*, U.S.P.Q. 870 (Fed. Cir. 1985). The cited references do not provide this requisite suggestion of desirability.

As defined by claims 1 and 30, the controlled release pharmaceutical compositions according to the invention comprise at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848, a first intelligent polymer component, and a second intelligent polymer component having opposite wettability characteristics to the first intelligent polymer component. The first and second polymer components are present in a ratio in the range of about 1:100 to about 100:1 by weight, and are effective for providing controlled sustained release of a pharmaceutically active substance from the composition for at least 20 hours. According to claim 1, the second intelligent polymer component comprises hydroxyethylcellulose (HEC) or a mixture of HEC and hydroxypropyl methyl cellulose (HPMC). According to claim 30, the first intelligent polymer component comprises ethyl cellulose (EC) and the second intelligent polymer component comprises HEC or HPMC, or a mixture of HEC and HPMC. Claim 30 also recites that the components are formulated as a homogenous matrix and the composition has a moisture content of less than 3%.

Applicants find no teaching or suggestion in the cited combination of references regarding a combination of first and second intelligent polymer components as presently claimed, particularly in combination with a pharmaceutically active substance as presently

claimed to produce a controlled sustained release of pharmaceutically active substance from a composition for at least 20 hours.

As previously noted, Lowey et al disclose a solid pharmaceutical composition in which the carrier consists essentially of HPMC or HPMC admixed with up to about 20% EC, which composition is humidified to a moisture content of from about 5 to about 25% by weight. Applicants find no teaching by Lowey et al relating to the combination of first and second intelligent polymer components as required by claim 1 or the combination of first and second intelligent polymer components as recited in claim 30 in a composition having a moisture content of less than 3%. The deficiencies of Lowey et al are not resolved by Stupak et al's teaching of excipients or Takashima et al's teachings of cellulose derivatives.

Interchangeability of Polymers

Takashima et al teach the use of cellulose derivatives as binders in different preparations. Takashima et al use cellulose derivatives dissolved in aqueous solution, including HPMC and EC, as binders to wet the surfaces of tumbling drug-containing particles. A sustained release preparation was obtained only by heat treating the granules after treatment with oil, fat or wax hydrophobic solid material. The sustained release characteristics of the preparations taught by Takashima are due to the oil, fat or wax solid material present in the composition and not to the cellulose derivatives used as binders or wetting agents in the preparations. This is exemplified in Figs. 1-7 of Takashima et al where cellulose derivatives were used as binders. Control preparation #1 made with cellulose derivatives alone released 100% of the drug in less than 10 minutes, i.e., the release was not controlled as the effect/profile and extent of drug release was dependent on the type of hydrophobic solid material (oil/fat/wax) used. In the preparation exemplified in Figure 1, castor oil was used, while in the preparation exemplified in Figs. 2 and 3, carnuba wax and stearic acid were used, respectively.

The Takashima et al Figures exemplify that as the concentration of oil/fat/wax is changed, the amount of drug released changes accordingly. When binder type and binder (HPC or EC) concentration is kept constant while at the same time the wax/oil/fat content is kept constant, the controlled release or sustained release depends on the concentration and type of hydrophobic solid material, i.e., wax/oil/fat and not on the type or concentration of the binder. Furthermore, the results in the Figures clearly indicate that the release modifying or sustained release agents (i.e. wax/oil/fat) are not interchageable even though they are used for the same purpose. This is clearly indicated in Figures 1, 2 and 3 where the same concentrations of castor oil, carnuba wax and stearic acid show significant differences in their sustained or controlled release profile, rates and extent of drug release. Thus, these agents are not interchangeable for the very same purpose. As such, Takashima et al do not teach that cellulose derivatives are known and interchangeable. Takashima et al in fact teach that the oil/wax/hyphobic solid materials are not interchangeable. Takashima et al nowhere teach, suggest or demonstrate that cellulose derivatives are interchangeable for the same purpose, especially that of controlled release.

Contrary to the Examiner's assertions, the Applicants have been able to demonstrate that cellulose derivatives are not interchangeable for the same very purpose, more specifically, hydroxypropylmethyl cellulose (HPMC), ethylcellulose (EC), and hydroxyethyl cellulose (HEC) are not interchangeable for the very same purpose. This is supported by the data in Tables 1 and 2 and in Figure 1 set forth in the Declaration Under 37 C.F.R. 1.132 of the coinventors.

More particularly, the Declaration describes experiments conducted by the coinventors, or under their direction and control, wherein HPMC, EC and HEC were respectively employed in drug active-containing compositions. As shown in Table 2 and Figure 1, in the Declaration, the amount of drug released in 1 hour is 17% for HPMC, 60% for HEC and 88% for EC. It was also observed that EC tablets broke up in 30 minutes. The

time taken for 70% of the drug (i.e., $T_{70\%}$) to be released was about 9 hours for HPMC, 4 hours for HEC and 30 minutes for EC. These results clearly indicate that HPMC, HEC and EC are not interchangeable, particularly in controlled release compositions. Moreover, these results do not teach or suggest that the combinations recited in claims 1 and 3 can provide compositions exhibiting controlled release of at least 20 hours.

In re Kerkhoven, 205 U.S.P.Q. 1069, 1072 (CCPA 1980), actually supports the Applicants' position since the combination of Stupak et al and Takashima et al does not teach usefulness for the same purpose, as discussed *supra* in respect for Takashima et al. Again, the teachings of Takashima et al with respect to combining HPMC and HEC is not relevant to sustained release characteristics. Thus, the teachings of Takashima et al would lead one of ordinary skill in the art to use wax/oils and/or solid hydrophobic materials for sustained release characteristics rather than cellulose derivatives. One of skill in the art would not expect to achieve any success in the provision of a sustained release composition having a release period of over 20 hrs relying on the teachings of the cited references.

The Examiner states that the present claims recite an extended release of up to at least 20 hours and that Lowey et al's teaching of up to 8 hours reads on this limitation. While Lowey et al may teach a release profile of up to 8 hours, they do not teach or suggest at least 20 hours. Furthermore, Lowey et al do not suggest how one would change the amounts of HPMC and EC employed to accomplish at least 20 hours of extended controlled release. Again, the teachings of Takashima et al would lead one to use oils or waxes to provide extended release characteristics and certainly not cellulose derivatives as discussed *supra*. Thus, these showings in the Declaration establish that the cellulose materials are not interchangeable and that the claimed compositions exhibit significant and unexpected improvement over Lowery et al.

Moreover, the Examiner asserts that there is no critical difference between 3% and 5% moisture content as recited in claim 30. However, the Applicants provide showings in

the Declaration demonstrating important differences between the claimed less than 3% moisture content and the lower limit 5% moisture content of Lowey et al. The results illustrated in Figs. 2-7 included in the Declaration from the Applicants' experimental work show the effect of moisture content of compositions according to the invention in the form of granulations and tablets on (i) Geometric mean granule diameter, (ii) Hausner ratio, (iii) Compressibility index, (iv) Friability, (v) Tablet hardness, and (vi) Tap density. Overall, the results indicate that the higher the moisture content, the less desirable characteristics are provided for the composition.

With respect to Figure 2, the role of granule size is very critical in the manufacturing process. Size affects mixing uniformity and content uniformity. Flowability of granules is also affected. Criticality was found at the 300-500 micron range of mean granule diameter, as well as with respect to tablet hardness and tensile strength. In the optimum 300-500 micron range, obtained at less than about 3% moisture content, apparently the granule size allows greater interparticle contact points per unit area, facilitating compression. A significantly greater mean granule diameter is obtained at 5% moisture.

The Hausner ratio measures the ability of the granule to flow during tabletting. Figure 3 shows that moisture content significantly affects the Hausner ratio, and thus the flowability of the granules. The sensitivity of this measurement is shown by the small scale of the Hausner ratio. Criticality was found at the less than 3% moisture levels, as optimal flow was observed at that level.

The compressibility index measures the ability of the granules to be compressed. There is a significant gradient between less than 3% and 5% as shown in Figure 4. Criticality was found at less than 3% moisture content. Optimum compressibility was observed at this level resulting in the minimum acceptable tablet hardness and tensile strength.

With respect to friability, there is a significant gradient between less than 3% and 5%, as shown in Figure 5. Criticality was found with regard to friability as less than 3% moisture

gave less friable tablets that were easy to coat without abrasion or breaking during the coating process.

Moisture content significantly affect the hardness of a tablet as shown in Figure 6. There is an optimum level of hardness below which the performance of a tablet is compromised. This critical level was found to be reached at less than 3% moisture content. At 5% moisture content and greater tablet hardness drops significantly to an unacceptable level. Finally, moisture content as shown in Figure 7 significantly affects the tap or packing density of a granule bed. The higher the moisture content, the lower the tap density. An optimum level of packing density was found, below which the physical performance of a granule is compromised. This critical level was found to be reached at less than 3% moisture content. At 5% moisture content and greater, the tap density drops significantly to an unacceptable level resulting in a bulky, more porous granule that needs more space during processing and filling operations.

An understanding of the phenomenology of swelling and the swelling kinetic theory of gels indicates that high moisture content results in the loss of some of a gel's properties and hence its drug release retardant property. The rate of swelling or shrinking of water containing gels or gels with high moisture content is much slower than for dryer gels. Consequently, having lost some of their gelling properties prior to introduction to the gastroinstestinal tract (GiT), high moisture content polymeric carriers are not suitable candidates as carriers for extended release (>24 hours) or once daily application of oral medicaments. This loss of activity may explain why Lowey et al's invention teaches a prolonged drug release of only 1-8 hours and use as a lozenge.

Finally, the Declaration indicates that criticality was observed with regards to stability for certain moisture sensitive drug products. Moisture contents of less than 3% resulted in a more stable product than moisture contents of 5% and higher. The higher moisture content may lead to degradation during storage.

This data provided clearly and unequivocally demonstrates a substantial difference in a moisture content of 3% as recited in claim 30 and 5%. Thus, the Declaration further demonstrates the significant and unexpected improvements of the claimed compositions over the cited prior art.

The Applicants have surprisingly found that the presently claimed combinations as recited in claims 1 and 30 provide for sustained therapeutic effects for at least 20 hours with only a single dose and without any food effect. Such is provided by the amount and type of cellulose derivatives recited in claims 1 and 30. The presently claimed invention is also easy and inexpensive to manufacture and more efficient in providing a sustained release of pharmaceutical agents than known controlled delivery systems. There has been a long felt need to provide a simple to make, cost-efficient extended release composition that could be used for a variety of different pharmaceutical actives and provide for a release effect of at least 20 hours.

In view of the above submitted arguments, it is evident that the cited combination of the teachings of the references does not suggest to one skilled in the art that such specific elements of each reference may be combined to provide the presently claimed compositions. Furthermore, Applicants find no teachings in any of the cited references which would lead one skilled in the art to expect that any such combination of selected teachings would lead to a successful extended release formulation as presently claimed. For these reasons, the presently rejected claims cannot be considered to be obvious in view of the combined teachings of the cited art.

It is believed that the above represents a complete response to the rejection under 35 U.S.C. §103(a) and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

Holly D. Kozlowski, Reg. No. 30,468
Attorney for Applicants
1900 Chemed Center
255 E. Fifth Street
Cincinnati, Ohio 45202
Tel: (513) 977-8568
Fax: (513) 977-8141

VERSION WITH MARKINGS SHOWING CHANGES MADE

1. (Third Amendment) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising hydroxyethylcellulose or a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for [up to] at least 20 hours.

30. (Twice Amended) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component comprising ethylcellulose

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising hydroxyethylcellulose, or hydroxypropyl methyl cellulose, or a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose<u>, the first and second</u> polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight, wherein said first and second polymer components are effective for providing

controlled sustained release of said pharmaceutically active substance from said composition for [up to] at least 20 hours; and

wherein components (a), (b) and (c) are formulated as a homogeneous matrix and said composition has a moisture content of less than 3%.

819253v1
10914-11